

Specifically, the Examiner contends that the specification "fails to establish the utility of the claimed  $\alpha$ 4 $\beta$ 1-specific antibodies as therapeutic agents to block lymphocyte adherence and migration in human patients." The Examiner maintains that the "asserted utility of the claimed methods for treating humans would [not] be believable *prima facie* to persons of skill in the art in view of the contemporary knowledge in the art." Finally, the Examiner asserts that the Patent Office can require examples "if there is strong evidence that the claimed invention does not work." Applicant traverses.

The Examiner's assertion of lack of utility fails for the following reasons. First, the Examiner has not established a *prima facie* case of non-utility as required by MPEP § 608.01(p). As detailed below, the documents cited by the Examiner do not establish that case. Nor has the Examiner addressed the evidence of utility highlighted by applicant in the December 7, 1993 Response to Office Action. Further, the Examiner's reference to the action of the FDA is inapposite to the utility issue.

Second, despite the absence of a *prima facie* case of non-utility, the *in vivo* data submitted herewith confirm the utility of the invention as disclosed in the application and the *in vitro* data set forth therein.

Claims 1-5 recite methods for inhibiting the adherence of lymphocytes to endothelial cells comprising exposing the lymphocytes to an antibody or an antigen-binding fragment thereof that binds to  $\alpha$ 4 $\beta$ 1. Claims 32 and 34-36 recite methods for preventing lymphocyte migration into tissues, again comprising the use of an anti- $\alpha$ 4 $\beta$ 1 antibody or antigen-binding fragment thereof.

Applicant has provided in vitro examples of the ability of anti- $\alpha 4\beta 1$  monoclonal antibodies to block the adhesion of lymphocytes to endothelial cells in the application (see Example 7, page 45). As pointed out in applicant's December 7, 1993 Response, these examples relate to a particular in vitro system employing human cell types. Specifically, applicant's in vitro system uses Jurkat (human T cell leukemia), Ramos (human B cell leukemia) and other human lymphocytes and human umbilical vein endothelial cells ("HUEVs") (see specification, page 46, lines 2-11). As detailed in that Response, one of skill in the art would expect the demonstrated ability of anti- $\alpha 4\beta 1$  monoclonal antibodies to prevent the adhesion of human lymphocytes to human endothelial cells in this particular in vitro system to be predictive of the activity of these antibodies in humans. The Examiner has cited no evidence to the contrary.

Instead, the Examiner's "strong evidence" for the asserted lack of utility includes: 1) W. J. Harris and S. Emery, "Therapeutic antibodies - the coming of age," Trends in Biotechnology, 11, pp. 42-44 (1993) ("Harris"), 2) T. A. Waldmann, "Monoclonal Antibodies in Diagnosis and Therapy," Science, 252, pp. 1657-1662 (1991) ("Waldmann") and 3) the low Food and Drug Administration ("FDA") approval rate for therapeutic antibodies. None of this "evidence" supports the Examiner's conclusion of non-utility of antibody-based therapies. If anything, the cited documents demonstrate that the asserted utility of applicant's invention would be believable to one of skill in the art.

Harris summarizes four approaches to the development of monoclonal antibodies for therapy, focusing on the methodology of each approach. Harris makes only two

brief references to any experimental results, neither of which constitutes "strong evidence" that applicant's invention would not work. Instead, those results report the greatly reduced immunogenicity of chimeric and humanized antibodies (see page 42, col. 3 and page 43, col. 1). Further, Harris states that "an important conclusion, drawn from all available data, is that chimaeric antibodies are non-toxic" (page 42, col. 3).

Waldmann reviews in vivo use of monoclonal antibodies for diagnosis and therapy with special reference to recent advances in that area. In supposed support of the § 101 rejection, the Examiner repeatedly misinterprets Waldmann. For example, the Examiner asserts that Waldmann teaches generally that monoclonal antibody therapy in humans is not effective -- due to the pharmacokinetics of rodent antibodies in humans and human anti-mouse antibody ("HAMA") responses. However, Waldmann states only that "unmodified murine monoclonal antibodies" are immunogenic in humans. Waldmann goes on to state that "murine antibodies are of value in therapy of human diseases" though their effectiveness is limited. Waldmann then describes modifications that have been shown to circumvent the difficulties encountered with unmodified rodent antibodies (see page 1658, col.2). The modifications described by Waldmann are the same as those disclosed in the present application (see specification, page 17, lines 17-25).

Again, the Examiner asserts that Waldmann indicates that in vitro and animal model studies "have not correlated well with in vivo clinical trial results in patients." Waldmann makes no such generalization. The Examiner has taken this statement out of its very narrow

context, namely, that the results with first generation immunotoxins in patients with cancer were disappointing in light of in vitro and animal studies. Waldmann goes on to state that the use of such antibodies in benign diseases, or of modified immunotoxins in cancer patients, was encouraging (page 1660, col. 2).

Yet again, the Examiner asserts that Waldmann cannot provide evidence of the utility of applicant's invention because it is "written in terms of promise and potential, not efficacious working examples in humans." In fact, Waldmann, cites no fewer than fourteen studies demonstrating effective in vivo therapies with monoclonal antibodies in humans.

In the December 7, 1993 Response, applicant directed the Examiner to specific quotations in Harris and Waldmann that support the asserted utility of applicant's invention and demonstrate the Examiner's mischaracterization of those documents. Applicant also discussed and submitted R. Thorpe, "Monoclonal Antibodies: Clinical and Regulatory Issues," Trends in Biotechnology, 11, pp. 40-42 (1993) which, reporting the results of a 1992 monoclonal antibody research meeting, concluded that: "[o]verall, the consensus of the meeting was that monoclonal antibodies are useful therapeutic and in vivo diagnostic agents." The Examiner has not responded to applicant's earlier comments. However, the Examiner cannot maintain the § 101 rejection on the basis of his own interpretation of the cited documents, while ignoring applicant's specific contradictory evidence.

The Examiner also ignores the more than twenty specific and positive examples of in vivo therapeutic use of monoclonal antibodies in Waldmann. Moreover, many of these

examples involve antibodies, such as those of applicant's invention, that bind to lymphocyte surface molecules. Accordingly, Waldmann clearly provides evidence that the in vivo utility of applicant's methods for preventing lymphocyte adhesion to endothelial cells would be believable to one of skill in the art.

Finally, the Examiner points to the low rate of FDA approval of antibodies for therapy as "strong evidence" that applicant's invention would not work. The FDA standards clearly serve a different purpose than that served by the patent laws. While FDA approval and supporting data may confirm the utility of an invention, absence of FDA approval or such data by no means indicates lack of utility. The approval of a new treatment by the FDA may be delayed for any number of reasons unrelated to efficacy. Accordingly, the action or inaction of the FDA in the area of antibody-based human therapies cannot be viewed as "strong evidence" that applicant's invention would not work.

The Examiner's conclusion of non-utility is totally unsupported by any document of record. In fact, the cited documents support the utility of applicant's invention. "If the asserted utility of a compound is believable on its face to persons skilled in the art in view of the contemporary knowledge in the art, then the burden is on the examiner to give adequate support for lack of utility...." MPEP § 608.01(p) The Examiner has provided no such support. Accordingly, the § 101 claim rejection should be withdrawn.

Applicant believes that no further proof of the utility of the methods of this invention is required because the Examiner has failed to establish a prima facie case of non-utility. Nevertheless, to expedite the prosecution of

this application, applicant submits the following document as confirmation of the in vivo utility. T. A. Yednock et al., "Prevention of Experimental Autoimmune Encephalomyelitis by Antibodies Against  $\alpha 4\beta 1$  Integrin," Nature, 356, pp. 63-66 (1992) ("Yednock") (copy enclosed) sets forth data obtained using various antibodies useful in the methods of this invention in both an in vitro adhesion assay and an in vivo study in a rat model for multiple sclerosis.\*

As discussed in Yednock, experimental autoimmune encephalomyelitis ("EAE") is an inflammatory condition of the central nervous system ("CNS"). In EAE, as in multiple sclerosis, leukocytes migrate from the circulation to the brain and spinal chord, resulting in impaired nerve conduction and paralysis (see page 63, col. 1). Adhesion of leukocytes to inflamed brain endothelium is the first step in their entry into the CNS.

In Yednock, sections of brain from rats with EAE were used in an in vitro assay to test the ability of various anti- $\alpha 4\beta 1$  monoclonal antibodies to inhibit the adhesion of lymphocytes to endothelial cells. While untreated human lymphocytes bound to the endothelium of exposed, inflamed venules and arterioles, the adhesion of these cells was almost entirely blocked by treatment with anti- $\alpha 4$  or anti- $\beta 1$  monoclonal antibodies. Yednock's in vitro section assay using endothelium that was activated in vivo confirms and extends the observations from previous in vitro adhesion assays involving cultured endothelium.

Having shown that the anti- $\alpha 4$  integrin antibody, HP2/1, blocked lymphocyte binding to EAE endothelium in

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\* Applicant has enclosed a facsimile copy of Yednock herewith and will forward an original as soon as it is received.

vitro, Yednock also tested the effect of this antibody in vivo. The brainstems of EAE animals given one intraperitoneal injection of HP2/1 showed no detectable lymphocyte infiltration (see page 66, col. 1 and Figure 3). In contrast, the brainstems of control animals showed extensive lymphocyte infiltration. In view of the in vitro inhibition of lymphocyte adhesion by anti- $\alpha 4$  antibody, Yednock concludes that the in vivo antibody treatment blocked the migration of lymphocytes into the inflamed brain.

Applicant expressly discloses the utility of the methods of the present invention in the treatment of diseases involving autoimmune responses including multiple sclerosis (see page 10, lines 30-33 and page 23, lines 9-16). Yednock's in vitro results directly confirm the in vitro results disclosed in the present application. Further, the combination of in vitro and in vivo results in Yednock confirm that applicant's in vitro assays are predictive of the in vivo utility of anti- $\alpha 4\beta 1$  monoclonal antibodies in the present invention. Moreover, because EAE in rats is an art-recognized model for human multiple sclerosis, Yednock exemplifies the "appropriately correlated" animal tests described in MPEP 608.01(p) and confirms the utility of the methods of the present invention in human therapy.

The specification stands objected to and claims 1-5, 32 and 34-36 stand rejected under 35 U.S.C. § 112, first paragraph, for "failing to provide an enabling disclosure." Specifically, the Examiner asserts that applicant has not disclosed how to use  $\alpha 4\beta 1$ -specific antibodies therapeutically in humans as there are no examples of in vivo immunotherapy using these antibodies. Further, the

Examiner contends that it would require "undue experimentation" to practice the invention using the teaching of the specification alone. Applicant traverses.

As disclosed in the specification, applicant's invention has utility in the suppression of the immune and autoimmune responses in a wide range of diseases, including allergy, asthma and multiple sclerosis (see specification, page 23, lines 12-20). Applicant also generally describes the systemic inhibition of lymphocyte migration into tissues by the administration of a monoclonal antibody that binds to  $\alpha 4\beta 1$  by any route, including intraperitoneally, in a suitable pharmacologic carrier (see specification, page 23, line 21 to page 24, line 5). Yednock, in fact, shows the inhibition of lymphocyte migration using the same techniques (see page 66, col. 1 and the legend to Fig. 3). Thus, Yednock confirms that persons of skill in the art would know how to practice applicant's invention without undue experimentation.

Furthermore, the diseases targeted by applicant's invention are not new. There exists a large body of information on the treatment of these diseases which would be known to persons of skill in art. Similarly, the techniques of monoclonal antibody therapy were known in the art (see Waldmann and reviews cited therein, copies enclosed).

Applicant has provided examples demonstrating the ability of anti- $\alpha 4\beta 1$  antibodies to completely block the adhesion of human lymphocytes to human endothelial cells (see Example 7, page 45). Further, the specification discloses that the antibodies of the invention may be used with a pharmacological carrier and may be administered by any route (see page 24, lines 3-8 and page 23, lines 30-

33). Finally, the specification (page 17, line 17 to page 18, line 18) provides guidance regarding antibodies for therapeutic use by way of general discussion and five specific references from the art.

In view of the knowledge in the art as to the methods of treatment of immune diseases and the therapeutic use of monoclonal antibodies and the teachings of this application, one of skill in the art of treating immune diseases would be able to practice the claimed invention without undue experimentation. Accordingly, the claim rejection and objection to the specification under 35 U.S.C. § 112, first paragraph, should be withdrawn.

Claims 1-5, 32 and 34-36 stand rejected under 35 U.S.C. § 112, first and second paragraphs, as "indefinite in the recitation of an antigen-binding 'region'" because the characteristics of such "'region'" are not known.

In accordance with the Examiner's suggestion, applicant has amended claims 1 and 32, and the claims depending therefrom, to recite an antigen-binding "fragment" rather than "region." Support for this amendment is provided in the specification at page 17, lines 27-30, page 17, line 35 to page 18, line 5, page 22, lines 17-22 and page 25, lines 19-21. These amendments do not introduce new matter. In view of these amendments, applicant requests that the Examiner withdraw the rejection under 35 U.S.C. § 112, first and second paragraphs.

Applicant acknowledges with appreciation the Examiner's withdrawal of the previous rejections under 35 U.S.C. § 112, first paragraph, regarding the deposits of biological materials, § 112, first and second paragraphs and § 103.

In view of the above, applicant requests entry of the claim amendments, withdrawal of the claim rejections and allowance of claims 1-5, 32 and 34-36.

Respectfully submitted,

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